ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 November 1998 (18.11.98)	
International application No. PCT/US98/06144	**Applicant's or agent's file reference** 3064/PCT
International filing date (day/month/year) 30 March 1998 (30.03.98)	**Priority date** (day/month/year) 04 April 1997 (04.04.97)
Applicant TREMONT, Samuel, J.	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   21 October 1998 (21.10.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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Facsimile No.: (41-22) 740.14.35

Authorized officer

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A2

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Published
Without international search report and to be republished upon receipt of that report.

(54) Title: HYDROLYSABLE DELIVERY SYSTEM USING CROSS–LINKED POLYMERIC RESINS AS VEHICLES

(57) Abstract

This invention provides a method of preparing a polymeric delivery system for active ingredients. The delivery system is formed either by attaching the active ingredient to a linker through a hydrolyzable covalent bond, then forming a covalent bond between the linker and a portion of the subunits of a cross–linked polymer, or by attaching a linker to a portion of the subunits of a cross–linked polymer, then attaching the active ingredient to the polymer–linker combination through a hydrolyzable covalent bond. The invention also provides a delivery system comprising an active ingredient covalently bonded through a hydrolyzale covalent bond to a linker, which is in turn covalently bonded to a portion of subunits of a cross–linked polymer.

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TENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
3064/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 06144	30/03/1998	04/04/1997
Applicant		
MONSANTO COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 06144

Box I Observations wh re certain claims w r f und unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-19 in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06144

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48 //A61K31/415

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAROBE J ET AL: "NEPHELOMETRIC ASSAY OF IMMUNOGLOBULIN G CHEMICALLY BOUND TO CHLOROMETHYL STYRENE BEADS" POLYMERS FOR ADVANCED TECHNOLOGIES, vol. 7, no. 9, 1 September 1996, pages 749-753, XP000625571 see paragraph METHODS see page 751, right-hand column - page 752, left-hand column --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 1998	20/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 98/06144

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE DISSERTATION ABSTRACTS University Microfilms International AN: AAD93-13414, 1993 PARSONS-WINGERTER, PATRICIA ANN: "COOPERATIVITY IN HEPATOCYTE CULTURE FROM CELL-CELL AND CELL-SUBSTRATE INTERACTIONS (CELL CELL INTERACTIONS, BIOACTIVE POLYMER, COLLAGEN GELS)" XP002079757 see abstract & DISSERTATION ABSTRACTS INTERNATIONAL, vol. 54, no. 01, page 368	1-19
Y	BLOSSEY E C ET AL: "SYNTHESIS REACTIONS AND CARBON-13 FT NMR SPECTROSCOPY OF POLYMER-BOUND STEROIDS." J ORG CHEM 1990, VOL. 55, NO. 15, PAGES 4664-4668, XP002079753 see abstract see page 4667 - page 4668	1-19
Y	LARSEN, CLAUS ET AL: "Macromolecular prodrugs. IX. The release kinetics of metronidazole from various dextran dicarboxylic acid hemiester conjugates in aqueous buffer, human plasma and in pig liver homogenate" ACTA PHARM. SUEC. 1988, VOL. 25, NO. 1, PAGE(S) 1-14, XP002079754 see abstract see tables	1-19
Y	TESLARIU, E. ET AL: "The investigations on some pharmacokinetic properties of metronidazole bound on polymeric support" WORLD MEET. PHARM., BIOPHARM. PHARM. TECHNOL., 1ST, PAGES 903-904 PUBLISHER: APGI, CHATENAY MALABRY, FR., XP002079755 see page 904	1-19
Y	DUMITRIU, SEVERIAN ET AL: "Bioactive polymers. 58. Synthesis and characterization of a polymeric prodrug based on 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole" CHIM. OGGI, 09-1988, NO. 9, PAGE(S) 59-63, XP002079756 see abstract see table 1 see page 63	1-19

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
Monsanto 28 769		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/06144	30/03/1998	04/04/1997
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant MONSANTO COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/10/1998	20.07.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Pilling, S Telephone No. (+49-89) 2399 8461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/06144

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20	as originally filed			
Claims, No.:				
3-13,19 (part)	as originally filed			
1,2,14-18, 19 (part)	as received on	02/07/1999	with letter of	30/06/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V

1. The present application relates to hydrolysable systems for delivering an active agent (Claims 15 to 19) and methods for their preparation (Claims 1 to 14).

2. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D6 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

Claims 15 to 19; hydrolysable systems for delivering an active agent

3. Document D3 (E C Blossey et al, J. Org. Chem.,1990, Vol. 55, No. 15, pp 4664-4668) discloses attachment of cholic acid derivatives to polymers using cross linkers in order to carry out synthetic chemical transformations. In these systems, the cholic acid derivative is bonded via the carboxylic acid group thereof to the hydroxyl group of *the p*-alkoxybenzyl-cross linked polystyrene resin *i.e.* **HOCH_2-C_6H_4-OCH_2-C_6H_4-cross linked polystyrene resin,** (see page 4668 in D3 with reference to the "*Polymer-Spacer-Dehydrocholate 4*").

4. Thus, on bonding of said cholic acid derivative, the delivery system of document D3 comprises an active ingredient, *i.e.* the cholic acid derivative, and a hydrolysable covalent bond, *i.e.* an ester bond, as defined in Claim 15. If the linker (as further defined in present Claim 15) is taken to be the initial part of the *p*-alkoxybenzyl group only, *i.e.* **$HOCH_2$-C_6H_4-.....,** then said linker is joined to the remainder of the *p*-alkoxybenzyl moiety, *i.e.* **.....-OCH_2-C_6H_4-cross linked polystyrene,** via an oxygen-carbon bond.

5. Alternatively if the linker group of document D3 is taken to be the entire *p*-alkoxybenzyl group, the linker would be bonded to the polymer via a carbon to carbon covalent bond

6. Thus, the subject matter of Claim 15 differs from the prior art in the present attachment of the linker to the polymer is via one of a *"a nitrogen-carbon bond, a sulfur-carbon bond and a phosphorus-carbon bond"* instead of via a carbon-carbon or oxygen-carbon bond as taught in document D3.

7. Thus, the subject matter of Claims 15 to 19 is new (Article 33(2) PCT).

8. The following comments relate to inventive step of Claims 15 to 19; document D3 appears to be the closest prior art and (as indicated above) the difference between the subject matter of Claim 15 and the disclosure of document D3 is the present use of one of *"a nitrogen-carbon bond, a sulfur-carbon bond and a phosphorus-carbon bond"* instead of a carbon-carbon or oxygen-carbon bond as taught in document D3. In this regard, it is known that N-C, S-C or P-C bonds accept positive charges more readily than O-C bonds (or C-C bonds), *i.e.* it is easier to form ammonium, phosphonium or sulphonium ions than oxonium ions. This apparently facilitates swelling of the crosslinked polymer in aqueous environments (due probably to ionic interactions between the resulting charged groups and the water molecules). This swelling, in turn, facilitates hydrolysis of the hydrolysable covalent bond between the active ingredient and the linker and release of the active agent.

9. There is no suggestion in document D3 that the C-C or O-C bonds may be advantageously replaced by N-C, S-C or P-C bonds in order to facilitate release of the active ingredient from the delivery system. Indeed, the studies detailed in document D3 do not appear to essentially involve release of the active ingredient, *i.e.* the cholic acid from the polymer support.

10. Hence, it is not considered obvious on the basis of document D3 to arrive at the invention of present Claim 15. The subject matter of Claim 15 is, therefore, considered to be inventive (Article 33(3) PCT).

11. In reaching the above conclusions, the International Preliminary Examining Authority has also taken into account the disclosure of document D4 (C Larsen *et al*, Acta. Pharm. Suec., 1988, Vol. 25, No. 1, pp 1-14). Although this document describes delivery systems for active agents wherein said active agent is attached to a polymer via a linker, it is further noted that, in a similar way to document D3, there is no disclosure or suggestion of attachment of the linker to the polymer via N-C, S-C or P-C bonds. Furthermore, there is no suggestion in document D4 that the dextran polymers thereof should be crosslinked thereby rendering them non-absorbable by the body.

Claims 1 to 14; methods for the preparation of the above hydrolysable systems

12. In view of the above comments relating to novelty and inventive step of the delivery systems of Claims 15 to 19, it follows that methods of preparing said delivery systems must also be new and inventive. Hence, the subject matter of Claims 1 to 14 is considered to be new and inventive (Article 33(2) and 33(3) PCT)

SECTION VIII

13. The description has not yet been brought into agreement with the amended claims.

Article 34

CLAIM SHEET

1. A method for preparing a crosslinked polymeric selectively hydrolyzable delivery system for an active ingredient, said active ingredient containing a hydroxyl, CO_2H, amino, mercapto, or enolizable carbonyl moiety; said method comprising the steps of:

(a) selecting (i) the active ingredient, (ii) a linker, and (iii) a crosslinked polymer;

(b) forming a combination of (i) and (ii) or (ii) and (iii) by, respectively, attaching the active ingredient to a linker through a hydrolyzable covalent bond formed with the hydroxyl, CO_2H, amino, mercapto, or enolizable carbonyl moiety of the active ingredient to form an ester, carboxylic acid anhydride, amide, thioester, or enol ester; or forming a linker-polymer covalent bond selected from the group consisting of a nitrogen-carbon bond, a phosphorus-carbon bond and a sulfur-carbon bond between the linker and a portion of subunits of the crosslinked polymer; and

(c) forming the delivery system by combining the combination of (i) and (ii) with the crosslinked polymer or the combination of (ii) and (iii) with the active ingredient by, respectively, forming the linker-polymer covalent bond selected from the group consisting of a nitrogen-carbon bond, a phosphorus-carbon bond and a sulfur-carbon bond between the combination of (i) and (ii) and a portion of subunits of the crosslinked polymer or attaching the active ingredient to the combination of (ii) and (iii) through the hydrolyzable ester, carboxylic acid anhydride, amide, thioester or enol ester covalent bond.

2. The method of claim 1 wherein the hydrolyzable covalent bond is formed with a hydroxyl or a derivatized carboxylic acid substituent on the linker.

AMENDED SHEET

14. The method of claim 13 wherein the covalent bond through which the active ingredient is attached is formed with a hydroxyl moiety on the active ingredient.

15. A delivery system comprising: an active ingredient covalently bonded to a linker through a hydrolyzable covalent bond formed with a hydroxyl, CO2H, amino, mercapto, or enolizable carbonyl moiety of the active ingredient to produce, respectively, an ester, carboxylic acid anhydride, amide, thioester, or enol ester; said linker being covalently bonded to a portion of subunits of a crosslinked polymer through a linker-polymer covalent bond selected from the group consisting of a nitrogen-carbon bond, a sulfur-carbon bond, and a phosphorus-carbon bond.

16. The delivery system of claim 15 wherein the crosslinked polymer is selected from the group consisting of poly[(4-dialkylaminomethyl)styrene], poly[(3-dialkylaminomethyl)styrene], and mixtures of poly[(4-dialkylaminomethyl)styrene] and poly[(3-dialkylaminomethyl)styrene].

17. The delivery system of claim 16 wherein the crosslinked polymer is poly[(4-dimethylaminomethyl)styrene], poly[(3-dimethylaminomethyl)styrene], or a mixture thereof.

18. The delivery system of claim 17 wherein substantially all styrenic subunits of the crosslinked polystyrene polymer not bonded to the linker are substituted by quaternary ammonium salt moieties.

19. The delivery system of claim 18 wherein the active ingredient and the linker form a substituent on a 4-